NTP Research Concept: Bisphenol AF

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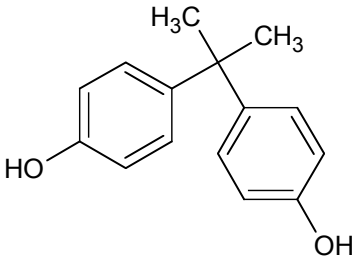
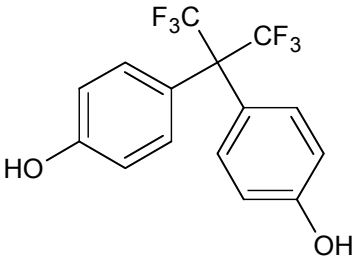
Background and Rationale



Bisphenol A



Bisphenol AF

Numerous toxicological effects have been associated with bisphenol A (BPA) in mammals depending upon the level of exposure, including effects on reproduction and development and other endocrine-related biological effects. The National Toxicology Program (NTP) recently reported *some concern* for effects on the brain, behavior, and prostate gland in fetuses, infants, and children at current human exposures to BPA. The NTP reviewed a number of chemicals structurally related to BPA for potential health hazard identification. Bisphenol AF (BPAF) was selected from that review and nominated by the National Institute of Environmental Health Sciences for toxicity studies based on its moderate production and use as a monomer for polyimides, polyamides, polyesters, polycarbonates, and other specialty polymers, and lack of adequate toxicity data. Similar to BPA, BPAF and some other members of this class of compounds have potential endocrine activity (http://ntp.niehs.nih.gov/go/33220).

US annual production of BPAF has been reported every four years from 1986-2002 at 10,000-500,000 pounds, which is classified as moderate production. Use information is very limited; however, BPAF is reportedly used as a monomer in polycarbonates and epoxy resins, and may be used in food-contact polymers. The National Institute for Occupational Safety and Health National Occupational Exposure Survey (1981-1983) estimated that 4388 employees (1460 females) were potentially exposed to BPAF; this number represented eight occupations in two industries. BPAF is predicted to be persistent in the environment, likely because of the presence of six fluorines in the molecule. In one study, BPAF was found in extracts of human female adipose tissue. Although the production and use, and presumably the magnitude of human exposure of BPAF are much lower than BPA, the results of some *in vitro* and *in vivo* screening assays suggest that BPAF may be a more potent synthetic estrogen than BPA. For example, in an estrogen luciferase reporter assay in MCF-7 cells, BPAF (EC50 of 0.05 μM) was approximately one order of magnitude more potent than BPA (EC50 of 0.63 μM). In an uterotrophic assay in immature female Sprague Dawley rats, daily subcutaneous injections of 200 mg/kg BPA for three days resulted in a 197% increase in the absolute blotted uterus weight compared to control, while exposure to 100 mg/kg BPAF resulted in a 337% increase. In addition to estrogenic effects, there is a limited amount of data suggesting other hormonal effects. BPAF demonstrated anti-

androgenic activity, inhibiting the activity of dihydrotestosterone in a luciferase reporter assay in NIH3T3 cells; the results of a Hershberger assay in castrated 7 week-old male Wistar Han rats exposed for 10 days by gavage did not confirm this in vitro anti-androgenicity. In a vitellogenin production assay in male carp hepatocytes, while BPAF alone demonstrated estrogenic activity, BPAF inhibited vitellogenin production by 17β-estradiol, demonstrating anti-estrogenic activity; a similar pattern was observed in the uterotrophic assay (BPAF ± ethinyl estradiol). The reported endocrine-related biological activities of BPA may result from interactions with other receptors, including estrogen-related receptor gamma (ERRγ); BPA is a very potent ligand of ERRγ. In a comparative study, the binding activity of BPAF was much lower (~35-fold) than that of BPA. The uterotrophic assay and Hershberger assays are the only in vivo studies reported in the literature for BPAF. These studies were designed and conducted to examine the hormonal activities of BPAF, rather than characterize the potential toxicities that may result from these activities.

Key Issues

Testing of BPAF is warranted based on its moderate production, reported estrogenic activity, possible persistence in the environment, lack of toxicity data, and structural similarity to BPA. Studies examining the estrogenic activities of BPA-related compounds have demonstrated that BPAF may display more potent estrogenicity in comparison to BPA specifically and to some other BPA-related compounds. There is also a more limited body of literature that suggests that other hormonal activities, such as anti-androgenicity and anti-estrogenicity, occur following exposure to BPAF. Thus, this research program shall evaluate the potential for BPAF to induce toxicity characteristic of the reported hormonal activities. Although BPAF is the first of the BPA-related compounds to be nominated for study, based primarily on its magnitude of production and its estrogenicity, the NTP is currently considering class approaches for evaluating the toxicity of other BPA-related compounds.

Proposed Approach

The overall goal of this research project is to better understand the potential toxicity of BPAF. Key components of this research program include the use of *in utero*/lactational exposures, testing over a wide range of doses, assessment of the disposition of BPAF, and the inclusion of endpoints to examine potential toxicity resulting from its hormonal activities. We hypothesize that potential toxic effects observed following exposure to BPAF will be characteristic of a synthetic estrogen. The route for these studies shall be oral. The tier one study (specific aim 1) will allow for an initial toxicological characterization of BPAF. Tier two studies (specific aims 2 and 3) will only be considered if review of the data from the tier one study and review of future information on the production and use of and human exposure to BPAF warrant further studies.

Specific Aims

Tier 1:
Specific Aim 1. Conduct an in utero-lactational (transgenerational) assay in rats, which involves exposure during gestation and lactation followed by exposure to sexual maturity. This study would provide a preliminary assessment of the potential for BPAF to induce reproductive or developmental toxicity and would also serve as a subchronic toxicity study with *in utero*/lactational initiation of dosing. This study shall include a positive control for estrogenic activity, characterization of the disposition of BPAF, and appropriate endpoints to detect endocrine-related phenotypic endpoints, including growth of the uterus, markers of onset of puberty and development of mammary tissue.

Tier 2:
Specific Aim 2. Conduct absorption, distribution, metabolism and elimination and toxicokinetic studies on BPAF. These studies will focus on characterizing changes in the metabolism of BPAF with life stage and the persistence of BPAF.

Specific Aim 3. Conduct multigenerational reproductive toxicity and developmental toxicity studies. These studies should include assessment of the disposition of BPAF. Additional endpoints may be added to the standard studies based on the results of the transgenerational study and the reported hormonal activities of BPAF.

Significance and Expected Outcome

Because there are no reported studies available that characterize the potential toxicity of BPAF or its disposition or toxicokinetics, the proposed research program will identify hazards associated with exposure to BPAF and further investigate the potential for BPAF to induce toxicity consistent with that of a synthetic estrogen.